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communicable disease agent(s), as required under §610.41 of this chapter, and the reason for that decision;

(ii) Where appropriate, the types of donation of blood or blood components that the autologous donor should not donate in the future; and

(iii) The results of tests for evidence of infection due to communicable disease agent(s), that were a basis for deferral under §610.41 of this chapter, including results of supplemental (i.e., additional, more specific) tests as required in §610.40(e) of this chapter.

(2) You must make reasonable attempts to notify the autologous donor's referring physician within 8 weeks after determining that the autologous donor is deferred as described in paragraph (a) of this section. You must document that you have successfully notified the autologous donor's referring physician or when you are unsuccessful that you have made reasonable attempts to notify the physician.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

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640.120 Alternative procedures.

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

SOURCE: 38 FR 32089, Nov. 20, 1973, unless otherwise noted.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Whole Blood

§ 640.1 Whole Blood.

The proper name of this product shall be Whole Blood. Whole Blood is defined as blood collected from human donors for transfusion to human recipients.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.2 General requirements.

(a) *Manufacturing responsibility.* All manufacturing of Whole Blood, including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Director, Center for Biologics Evaluation and Research, may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this subchapter.

(b) *Blood container.* The blood container shall not be entered prior to issue for any purpose except for blood collection or when the method of processing requires use of a different container. The container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(c) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) A segment is properly attached and has not been removed, except that blood lacking a properly attached segment may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within 6 hours after entering the container for sampling;

(3) The blood has been stored continuously at 1 to 6 °C and shipped between 1 and 10 °C;

(4) The blood is held for observation until a significant inspection consistent with the requirements of § 640.5(e) can be made.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 4015, Jan. 28, 1976; 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 15187, Apr. 18, 1984; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 53 FR 116, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 45371, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001; 66 FR 40889, Aug. 6, 2001; 67 FR 9587, Mar. 4, 2002]

§ 640.3 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall be made on the day of collection from the donor by means of medical history, a test for hemoglobin level, and such physical examination as appears necessary to a physician who shall be present on the premises when examinations are made, except that the suitability of donors may be determined when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who determine suitability of donors, and (2) maintains records indicating the name

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and qualifications of the person immediately in charge of the employees who determine the suitability of donors when a physician is not present on the premises.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f) of this section and for autologous donations, a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) For allogeneic donors, a blood hemoglobin level which shall be demonstrated to be no less than 12.5 grams (g) of hemoglobin per 100 milliliters (mL) of blood; or a hematocrit value of 38 percent, and for autologous donors, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent.

(4) Freedom from acute respiratory diseases;

(5) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the blood;

(6) Freedom from any disease transmissible by blood transfusion, insofar as can be determined by history and examinations indicated above; and

(7) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics.

(c) *Additional qualifications of donor; viral hepatitis.* No individual shall be used as a source of Whole Blood if he has—

(1) A history of viral hepatitis after the 11th birthday;

(2) A history of close contact within 12 months of donation with an individual having viral hepatitis;

(3) A history of having received within 12 months of donation, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establish-

ment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified under the provisions of this section, shall not be used as a source of Whole Blood unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

(e) [Reserved]

(f) *Qualifications; donations within less than 8 weeks.* A person may serve as a source of Whole Blood more than once in 8 weeks only if at the time of donation the person is examined and certified by a physician to be in good health, as indicated in part in paragraph (b) of this section.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 64 FR 45371, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

§ 640.4 Collection of the blood.

(a) *Supervision.* Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure. A physician shall be present on the premises when blood is being collected, except that blood may be collected when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who collect blood, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who collect blood when a physician is not present on the premises.

(b) *The donor center.* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the blood establishment and at any other place where the bleeding is performed.

(c) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container

when it is sterilized. In addition, all container and donor set surfaces that come in contact with blood used in the processing of Heparin Whole Blood shall be water repellent.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. Anticoagulant solutions shall be compounded and used according to a formula approved by the Director, Center for Biologics Evaluation and Research.

(e) *Donor identification.* Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor whose identity shall be established to the extent necessary for compliance with § 640.3.

(f) *Prevention of contamination of the blood.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) *Samples and segments for laboratory tests.* Samples and segments for laboratory tests shall meet the following standards:

(1) One or more segments shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(c)(2) and all segments shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all segments accompanying a unit of blood shall be collected at the time of filling the original blood container.

(3) All containers for all samples shall bear the donor's identification before collecting the samples.

(4) All segments accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamperproof manner that will conspicuously indicate removal and reattachment.

(5) Segments for compatibility testing shall contain blood mixed with the appropriate anticoagulant.

(h) *Storage.* Whole Blood must be placed in storage at a temperature between 1 and 6 °C immediately after collection unless the blood is to be further

processed into another component or the blood must be transported from the donor center to the processing laboratory. If transported, the blood must be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a temperature range between 1 and 10 °C until arrival at the processing laboratory. At the processing laboratory, the blood must be stored at a temperature between 1 and 6 °C. Blood from which a component is to be prepared must be held in an environment maintained at a temperature range specified for that component in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER.

[38 FR 32089, Nov. 20, 1973, as amended at 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001; 72 FR 45887, Aug. 16, 2007; 73 FR 7464, Feb. 8, 2008]

§ 640.5 Testing the blood.

All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood shall be negative to a serological test for syphilis.

(b) *Determination of blood group.* Each container of Whole Blood shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antisera are in agreement. Only those Anti-A and Anti-B Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-D Blood Grouping Reagent, is positive, the container may be

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labeled “Rh Positive.” If the test is negative, the results shall be confirmed by further testing which shall include tests for the “weak D (formerly D^u).” Blood may be labeled “Rh Negative” if further testing is negative. Units testing positive after additional more specific testing shall be labeled as “Rh Positive.” Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, this subchapter shall be used, and the technique used shall be that for which the reagent is specifically designed to be effective.

(d) *Sterility test.* Whole Blood intended for transfusion shall not be tested for sterility by a method that entails entering the final container before the blood is used for transfusion.

(e) *Inspection.* Whole Blood shall be inspected visually during storage and immediately prior to issue. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination the unit of Whole Blood shall not be issued for transfusion.

(f) *Test for communicable disease agents.* Whole Blood shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 53 FR 12764, Apr. 19, 1988; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001; 66 FR 40889, Aug. 6, 2001]

§ 640.6 Modifications of Whole Blood.

Upon approval by the Director, Center for Biologics Evaluation and Research, of a supplement to the biologics license application for Whole Blood a manufacturer may prepare Whole Blood from which the antihemophilic factor has been removed, provided the Whole Blood meets the applicable requirements of this subchapter and the following conditions are met:

(a) The antihemophilic factor shall be removed in accordance with paragraphs (a), (b), and (c) of § 640.52.

(b) Although the closed system between the red blood cells and plasma shall be maintained, the red blood cells shall be maintained between 1 and 6° C at all times, including that time when

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the plasma is being frozen for removal of the antihemophilic factor.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 45372, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999]

Subpart B—Red Blood Cells

§ 640.10 Red Blood Cells.

The proper name of this product shall be Red Blood Cells. The product is defined as red blood cells remaining after separating plasma from human blood.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 640.11 General requirements.

(a) *Storage.* Immediately after processing, the Red Blood Cells shall be placed in storage and maintained at a temperature between 1 and 6 °C.

(b) *Inspection.* The product shall be inspected immediately after separation of the plasma, periodically during storage, and at the time of issue. The product shall not be issued if there is any abnormality in color or physical appearance or if there is any indication of microbial contamination.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 42 FR 59878, Nov. 11, 1977; 50 FR 4139, Jan. 29, 1985]

§ 640.12 Suitability of donor.

The source blood for Red Blood Cells shall be obtained from a donor who meets the criteria for donor suitability prescribed in § 640.3.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 640.4.

(b) Source blood may also be derived from Whole Blood manufactured in accordance with applicable provisions of this subchapter.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999]

§ 640.14 Testing the blood.

Blood from which Red Blood Cells are prepared shall be tested as prescribed

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in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

[53 FR 117, Jan. 5, 1988, as amended at 66 FR 31165, June 11, 2001]

§ 640.15 Segments for testing.

Segments collected in integral tubing shall meet the following standards:

(a) One or more segments shall be provided with each unit of Whole Blood or Red Blood Cells when issued or re-issued.

(b) Before they are filled, all segments shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) All segments accompanying a unit of Red Blood Cells shall be filled at the time the blood is collected or at the time the final product is prepared.

[66 FR 40890, Aug. 6, 2001]

§ 640.16 Processing.

(a) *Separation.* Within the timeframe specified in the directions for use for the blood collecting, processing, and storage system used, Red Blood Cells may be prepared either by centrifugation, done in a manner that will not tend to increase the temperature of the blood, or by normal undisturbed sedimentation. A portion of the plasma sufficient to insure optimal cell preservation shall be left with the red cells except when a cryoprotective substance or additive solution is added for prolonged storage.

(b) *Sterile system.* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free.

(c) *Final containers.* Final containers used for Red Blood Cells shall be the original blood containers unless the method of processing requires a different container. The final container shall meet the requirements for blood containers prescribed in § 640.2(c). At the time of filing, if a different container is used, it shall be marked or identified by number or other symbol so as to relate it to the donor of that unit of red cells.

[38 FR 32089, Nov. 20, 1973, as amended at 43 FR 34460, Aug. 4, 1978; 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.17 Modifications for specific products.

Red Blood Cells Frozen: A cryophylactic substance may be added to the Red Blood Cells for extended manufacturers' storage at -65°C or colder, provided the manufacturer submits data considered by the Director, Center for Biologics Evaluation and Research, as adequately demonstrating through in vivo cell survival and other appropriate tests that the addition of the substance, the materials used and the processing methods results in a final product that meets the required standards of safety, purity, and potency for Red Blood Cells, and that the frozen product will maintain those properties for the prescribed dating period. Section 640.11 (a) and (b) do not apply while a cryophylactic substance is present.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 18292, May 3, 1976; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998]

Subpart C—Platelets

§ 640.20 Platelets.

(a) *Proper name and definition.* The proper name of this product shall be Platelets. The product is defined as platelets collected from one unit of blood and resuspended in an appropriate volume of original plasma, as prescribed in § 640.24(d).

(b) *Source.* The source material for Platelets is plasma which may be obtained by whole blood collection or by plateletpheresis.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985; 72 FR 45887, Aug. 16, 2007]

§ 640.21 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) [Reserved]

(c) Plateletpheresis donors must meet the criteria for suitability as prescribed in §§ 640.3 and 640.63(c)(6) or as described in an approved biologics license application (BLA) or an approved

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supplement to a BLA. Informed consent must be obtained as prescribed in § 640.61.

[40 FR 4304, Jan. 29, 1975, as amended at 49 FR 23834, June 8, 1984; 64 FR 56453, Oct. 20, 1999; 72 FR 45887, Aug. 16, 2007]

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in § 640.4.

(b) [Reserved]

(c) If plateletpheresis is used, the procedure for collection must be as prescribed in §§ 640.62, 640.64 (except paragraph (c)), and 640.65, or as described in an approved biologics license application (BLA) or an approved supplement to a BLA.

(d) The phlebotomy shall be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue.

[40 FR 4304, Jan. 29, 1975, as amended at 45 FR 27927, Apr. 25, 1980; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 64 FR 45372, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999; 72 FR 45887, Aug. 16, 2007]

§ 640.23 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Platelets shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

[40 FR 4304, Jan. 29, 1975, as amended at 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 31165, June 11, 2001]

§ 640.24 Processing.

(a) Separation of plasma and platelets and resuspension of the platelets must be in a closed system. Platelets must not be pooled during processing unless the platelets are pooled as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluation and Research.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20 and 24 °C unless it must be transported from the collection center to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20 and 24 °C until it arrives at the processing laboratory where it shall be held between 20 and 24 °C until the platelets are separated. The platelet concentrate shall be separated within 4 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(c) The time and speed of centrifugation must have been demonstrated to produce an unclumped product, without visible hemolysis, that yields a count of not less than 5.5×10^{10} platelets per unit in at least 75 percent of the units tested.

(d) The volume of original plasma used for resuspension of the platelets shall be determined by the maintenance of a pH of not less than 6.2 during the storage period. The pH shall be measured on a sample of platelets which has been stored for the maximum dating period at the selected storage temperature. One of the following storage temperatures shall be used continuously:

(1) 20 to 24 °C.

(2) 1 to 6 °C.

(e) Final containers used for Platelets shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, or efficacy of the product. At the time of filling, the final container shall be marked or identified by number so as to relate it to the donor.

[40 FR 4304, Jan. 29, 1975, as amended at 42 FR 10983, Feb. 25, 1977; 47 FR 49021, Oct. 29, 1982; 50 FR 4139, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001; 72 FR 45887, Aug. 16, 2007; 73 FR 7464, Feb. 8, 2008]

§ 640.25 General requirements.

(a) *Storage.* Immediately after re-suspension, Platelets shall be placed in storage at the selected temperature range. If stored at 20 to 24 °C, a continuous gentle agitation of the platelet concentrate shall be maintained throughout the storage period. Agitation is optional if stored at a temperature between 1 and 6 °C.

(b) *Quality control testing.* Each month four units prepared from different donors shall be tested at the end of the storage period as follows:

- (1) Platelet count.
- (2) pH of not less than 6.2 measured at the storage temperature of the unit.
- (3) Measurement of actual plasma volume.
- (4) If the results of the quality control testing indicate that the product does not meet the prescribed requirements, immediate corrective action shall be taken and a record maintained of such action.

(c) *Manufacturing responsibility.* All manufacturing of Platelets shall be performed at the same licensed establishment, except that the quality control testing under paragraph (b) of this section may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) and is qualified to perform platelet counts. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

- (1) The results of each test are received within 10 days of the preparation of the platelet concentrate, and are maintained by the establishment licensed for Platelets so that they may be reviewed by an authorized representative of the Food and Drug Administration.
- (2) The licensed Platelets manufacturer has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[40 FR 4304, Jan. 29, 1975, as amended at 47 FR 49021, Oct. 29, 1982; 49 FR 23834, June 8, 1984; 50 FR 4139, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 66 FR 1836, Jan. 10, 2001; 72 FR 45888, Aug. 16, 2007]

§ 640.27 Emergency provisions.

The use of the plateletpheresis procedure to obtain a product for a specific recipient may be at variance with §§ 640.21(c) and 640.22(c): *Provided, That:* (a) A licensed physician has determined that the recipient must be transfused with the platelets from a specific donor, and (b) the plateletpheresis procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician has certified in writing that the donor's health permits plateletpheresis.

[40 FR 53544, Nov. 18, 1975]

Subpart D—Plasma**§ 640.30 Plasma.**

(a) *Proper name and definition.* The proper name of this component is Plasma. The component is defined as:

(1) The fluid portion of one unit of human blood intended for intravenous use which is collected in a closed system, stabilized against clotting, and separated from the red cells; or

(2) The fluid portion of human blood intended for intravenous use which is prepared by apheresis methods as specified in the directions for use for the blood collecting, processing, and storage system including closed and open systems.

(b) *Source.* (1) Plasma shall be obtained by separating plasma from blood collected from blood donors or by plasmapheresis.

(2) Plasma may be obtained from a unit of Whole Blood collected by another licensed establishment.

[42 FR 59878, Nov. 22, 1977; 48 FR 13026, Mar. 29, 1983, as amended at 50 FR 4139, Jan. 29, 1985; 72 FR 45888, Aug. 16, 2007]

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§ 640.31 Suitability of donors.

(a) Whole blood donors shall meet the criteria for donor suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for donor suitability prescribed in § 640.63, excluding the phrase “other than malaria” in paragraph (c)(9) of that section. Informed consent shall be required as prescribed in § 640.61.

[42 FR 59878, Nov. 22, 1977, as amended at 64 FR 45372, Aug. 19, 1999]

§ 640.32 Collection of source material.

(a) Whole Blood must be collected, transported, and stored as prescribed in § 640.4. When whole blood is intended for Plasma, Fresh Frozen Plasma, and Liquid Plasma, until the plasma is removed, the whole blood must be maintained at a temperature between 1 and 6 °C or as specified in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, Center for Biologics Evaluations and Research. Whole blood intended for Platelet Rich Plasma must be maintained as prescribed in § 640.24 until the plasma is removed. The red blood cells must be placed in storage at a temperature between 1 and 6 °C immediately after the plasma is separated.

(b) Plasma obtained by plasmapheresis shall be collected as prescribed in §§ 640.62, 640.64 (except that paragraph (c)(3) of § 640.64 shall not apply), and § 640.65.

[42 FR 59878, Nov. 22, 1977, as amended at 45 FR 27927, Apr. 25, 1980; 50 FR 4139, Jan. 29, 1985; 64 FR 45372, Aug. 19, 1999; 72 FR 45888, Aug. 16, 2007]

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) Manufacturers of Plasma collected by plasmapheresis shall have testing and recordkeeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 59878, Nov. 22, 1977, as amended at 44 FR 17658, Mar. 23, 1979; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 66 FR 31165, June 11, 2001]

§ 640.34 Processing.

(a) *Plasma*. Plasma shall be separated from the red blood cells and shall be stored at -18 °C or colder within 6 hours after transfer to the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system unless the product is to be stored as Liquid Plasma.

(b) *Fresh Frozen Plasma*. Fresh frozen plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma must be separated from the red blood cells or collected by an apheresis procedure, and placed in a freezer within 8 hours or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system, and stored at -18 °C or colder.

(c) *Liquid Plasma*. Liquid Plasma shall be separated from the red blood cells and shall be stored at a temperature of 1 to 6 °C within 4 hours after filling the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(d) *Platelet Rich Plasma*. Platelet rich plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after completion of the phlebotomy or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system. The time and speed of the centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 and 24 °C immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24 °C.

(e) *Modifications of Plasma*. It is possible to separate Platelets and/or Cryoprecipitated AHF from Plasma. When these components are to be separated, the plasma shall be collected as described in § 640.32 for Plasma.

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as “Fresh Frozen Plasma,” if frozen within 6 hours after filling the final container or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system.

(2) Cryoprecipitated AHF shall be removed as prescribed in subpart F of part 640. The remaining plasma shall be labeled “Plasma, Cryoprecipitate Reduced.”

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled “Plasma, Cryoprecipitate Reduced.”

(f) *The final container.* (1) The final container shall have no color added to the plastic and shall be transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents.

(2) The final container material shall not interact with the contents, under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, potency, and effectiveness of the product.

(3) Prior to filling, the final container shall be identified by number so as to relate it to the donor.

(g) *The final product.* (1) The final product shall be inspected immediately after separation of the plasma and shall not be issued for transfusion if there is (i) any abnormality in color or physical appearance, or (ii) any indication of contamination.

(2) With the exception of Platelet Rich Plasma and Liquid Plasma the final product shall be inspected for evidence of thawing or breakage at the time of issuance, however, the containers need not be stored in a manner that shows evidence of thawing if records of continuous monitoring of the storage temperature establish that the temperature remained at -18°C or colder. If continuous monitoring of the product is not available, the final product shall be stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing.

(3) No preservative shall be added to the final product.

[42 FR 59878, Nov. 22, 1977, as amended at 43 FR 34460, Aug. 4 1978; 48 FR 13026, Mar. 29, 1983; 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001; 72 FR 45888, Aug. 16, 2007]

Subpart E [Reserved]

Subpart F—Cryoprecipitate

§ 640.50 Cryoprecipitated AHF.

(a) *Proper name and definition.* The proper name of this product shall be Cryoprecipitated AHF. The product is defined as a preparation of antihemophilic factor, which is obtained from a single unit of plasma collected and processed in a closed system.

(b) *Source.* The source material for Cryoprecipitated AHF shall be plasma which may be obtained by whole blood collection or by plasmapheresis.

[42 FR 21774, Apr. 29, 1977; 48 FR 13026, Mar. 29, 1983; as amended at 50 FR 4139, Jan. 29, 1985]

§ 640.51 Suitability of donors.

(a) Whole blood donors shall meet the criteria for suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for suitability prescribed in § 640.63, excluding the phrase “other than malaria” in paragraph (c) (9) of that section. Informed consent shall be required as prescribed in § 640.61.

[42 FR 21774, Apr. 29, 1977, as amended at 64 FR 45373, Aug. 19, 1999; 73 FR 49942, Aug. 25, 2008]

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

(b) If plasmapheresis is used, the procedure for collection shall be as prescribed in §§ 640.62, 640.64 (except that

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paragraph (c)(3) of that section shall not apply), and 640.65.

[42 FR 21774, Apr. 29, 1977, as amended by 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999]

§ 640.53 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Cryoprecipitated AHF shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (c).

(b) The tests shall be performed on a sample of blood collected at the time of collecting the source blood, and such sample container shall be labeled with the donor's number before the container is filled.

(c) Manufacturers of Cryoprecipitated AHF obtained from plasma collected by plasmapheresis shall have testing and record-keeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

[42 FR 21774, Apr. 29, 1977, as amended at 42 FR 37546, July 22, 1977; 42 FR 43063, Aug. 26, 1977; 50 FR 4139, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 66 FR 31165, June 11, 2001]

§ 640.54 Processing.

(a) *Processing the plasma.* (1) The plasma shall be separated from the red blood cells by centrifugation to obtain essentially cell-free plasma.

(2) The plasma shall be placed in a freezer within 8 hours after blood collection or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system. A combination of dry ice and organic solvent may be used for freezing: *Provided*, That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

(3) Immediately after separation and freezing of the plasma, the plasma shall be stored and maintained at -18°C or colder until thawing of the plasma for further processing to remove the Cryoprecipitated AHF.

(b) *Processing the final product.* (1) The Cryoprecipitated AHF shall be separated from the plasma by a procedure that has been shown to produce an average of no less than 80 units of antihemophilic factor per final container.

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(2) No diluent shall be added to the product by the manufacturer prior to freezing.

(3) The final container used for Cryoprecipitated AHF shall be colorless and transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under customary conditions of storage and use in such a manner as to have an adverse effect upon the safety, purity, potency and effectiveness of the product. At the time of filling, the final container shall be identified by a number so as to relate it to the donor.

[42 FR 21774, Apr. 29, 1977, as amended at 47 FR 15330, Apr. 9, 1982; 50 FR 4139, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.55 U.S. Standard preparation.

A U.S. Standard Antihemophilic Factor (Factor VIII) preparation may be obtained from the Center for Biologics Evaluation and Research, (HFM-407) (see mailing addresses in § 600.2 of this chapter) for use in the preparation of a working reference to be employed in a quality control potency test of Cryoprecipitated AHF.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005]

§ 640.56 Quality control test for potency.

(a) Quality control tests for potency of antihemophilic factor shall be conducted each month on at least four representative containers of Cryoprecipitated AHF.

(b) The results of each test are received by the establishment licensed for Cryoprecipitated AHF within 30 days of the preparation of the cryoprecipitated antihemophilic factor and are maintained at that establishment so that they may be reviewed by an authorized representative of the Food and Drug Administration.

(c) The quality control test for potency may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42

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U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in §610.63 of this chapter, provided the following conditions are met:

(1) The establishment licensed for Cryoprecipitated AHF has obtained a written agreement that the testing laboratory will permit an authorized representative of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(2) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

(d) If the average potency level of antihemophilic factor in the containers tested is less than 80 units of antihemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.

[42 FR 21774, Apr. 29, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001]

Subpart G—Source Plasma

§ 640.60 Source Plasma.

The proper name of the product shall be Source Plasma. The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

[41 FR 10768, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985]

§ 640.61 Informed consent.

The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if he is given the cells of another donor, and the hazards in-

volved if he is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

§ 640.62 Medical supervision.

A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor.

[66 FR 1837, Jan. 10, 2001]

§ 640.63 Suitability of donor.

(a) *Method of determining.* The suitability of a donor for Source Plasma shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability. Such determination shall be made on the day of collection from the donor by means of a medical history, tests, and such physical examination as appears necessary to the qualified licensed physician.

(b) *Initial medical examinations.* (1) Each donor shall be examined by a qualified licensed physician on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year.

(2)(i) A donor who is to be immunized for the production of high-titer plasma shall be examined by a qualified licensed physician. The medical examination shall be performed within no more than 1 week before the first immunization injection. The medical examination for plasmapheresis need not be repeated, if the first donation occurs within 3 weeks after the first injection.

(ii) A donor who is an active participant in a plasmapheresis program, and has been examined in accordance with paragraph (b)(1) of this section, need not be reexamined before immunization for the production of high-titer plasma.

(3) Each donor shall be certified to be in good health by the examining physician. The certification of good health shall be on a form supplied by the licensed establishment and shall indicate that the certification applies to the suitability of the individual to be a

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plasmapheresis donor and, when applicable, an immunized donor.

(c) *Qualification of donor.* Donors shall be in good health on the day of donation, as indicated in part by:

- (1) Normal temperature;
- (2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;
- (3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood or a hematocrit level of 38 percent;
- (4) A normal pulse rate;
- (5) A total serum or total plasma protein of no less than 6.0 grams per 100 milliliters of blood;
- (6) Weight, which shall be at least 110 pounds;
- (7) Freedom from acute respiratory diseases;
- (8) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the plasma;
- (9) Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examinations indicated in this section;
- (10) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics;
- (11) Freedom from a history of viral hepatitis after the 11th birthday;
- (12) Freedom from a history of close contact within 12 months of donation with an individual having viral hepatitis;
- (13) Freedom from a history of having received, within 12 months, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66.

(d) *General.* Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to

medical history questions, shall not be considered a suitable donor.

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks, unless:

- (1) The donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period;
- (2) The donor possesses an antibody that is (i) transitory, (ii) of a highly unusual or infrequent specificity, or (iii) of an unusually high titer; and
- (3) The special characteristics of the antibody and the need for plasmapheresis the donor are documented.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10768, Mar. 12, 1976; 43 FR 9805, Mar. 10, 1978; 43 FR 12311, Mar. 24, 1978; 46 FR 57480, Nov. 24, 1981; 50 FR 4140, Jan. 29, 1985; 64 FR 45373, Aug. 19, 1999; 66 FR 1837, Jan. 10, 2001; 66 FR 40890, Aug. 6, 2001]

§ 640.64 Collection of blood for Source Plasma.

(a) *Supervision.* All blood for the collection of Source Plasma shall be drawn from the donor by a qualified licensed physician or by persons under his supervision trained in the procedure.

(b) *Blood containers.* Blood containers and donor sets must be pyrogen-free, sterile, and identified by lot number.

(c) *The anticoagulant solution.* The anticoagulant solution must be sterile and pyrogen-free. Anticoagulant solutions must be compounded and used according to a formula that has been approved for the applicant by the Director, Center for Biologics Evaluation and Research.

(d) *Donor identification.* Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) *Prevention of contamination of the blood and plasma.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The

blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

[38 FR 32089, Nov. 20, 1973; 39 FR 13632, Apr. 16, 1974, as amended at 41 FR 10768, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 63 FR 16685, Apr. 6, 1998; 64 FR 56453, Oct. 20, 1999; 72 FR 45888, Aug. 16, 2007]

§ 640.65 Plasmapheresis.

(a) *Procedure-general.* The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the biologics license application.

(b) *Procedures-specific requirements.* The plasmapheresis procedure shall meet the following requirements:

(1)(i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided*, That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4-month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to ob-

tain a sample for testing as prescribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)(i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be non-reactive to a serologic test for syphilis, except as provided in paragraph (b)(2)(iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided*, That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided*, That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that

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continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,400 milliliters.

(6) No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case no more than 600 milliliters of whole blood shall be removed from the donor at one time.

(7) The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

(8) The volume of plasma collected during an automated plasmapheresis collection procedure shall be consistent with the volumes specifically approved by the Director, Center for Biologics Evaluation and Research, and

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collection shall not occur less than 2 days apart or more frequently than twice in a 7-day period.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 64 FR 45373, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999]

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection and scheduling of the injection of the antigen, and the evaluation of each donor's clinical response, shall be by a qualified licensed physician or physicians. The administration of the antigen may be performed by a licensed physician or a trained person under his supervision. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

[38 FR 32089, Nov. 20, 1973, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.67 Laboratory tests.

Each unit of Source Plasma shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

[66 FR 31165, June 11, 2001]

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the plasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to

exclude microorganisms and maintain a sterile system.

(b) *Final containers.* Final containers used for Source Plasma, whether integrally attached or separated from the original blood container, shall not be entered prior to issuance for any purpose except for filling with the plasma. Such containers shall be uncolored and hermetically sealed, and shall permit clear visibility of the contents. Final containers and their components shall not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination. Prior to filling, the final container shall be marked or identified by number or other symbol which will relate it directly to the donor.

(c) *Preservative.* Source Plasma shall not contain a preservative.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 50 FR 4140, Jan. 29, 1985]

§ 640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided*, That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma intended for manufacturing into noninjectable products is permitted: *Provided*, That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than -20°C , except for plasma collected as pro-

vided in § 640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma license application.

(c) *Inspection.* Source Plasma intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at -20°C or colder. If there is evidence that the storage temperature has not been maintained at -20°C or colder, the plasma may be relabeled and issued as provided in § 640.76(a).

(d) *Samples.* If samples are provided, they shall meet the following standards:

(1) Prior to filling, all samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All samples shall be representative of the contents of the final product or be collected from the donor at the time of filling the collection container.

(4) All samples shall be collected in a manner that does not contaminate the contents of the final container.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 41 FR 14367, Apr. 5, 1976; 50 FR 4140, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 45374, Aug. 19, 1999]

§ 640.70 Labeling.

(a) In addition to the labeling requirements of § 610.62 of this chapter, and in lieu of the requirements in §§ 606.121, 610.60, and 610.61 of this chapter, the following information shall appear on the label affixed to each container of Source Plasma:

(1) The proper name of the product.

(2) The statement "Caution: For Manufacturing Use Only" for products intended for further manufacturing into injectable products, or the statement, "Caution: For Use In Manufacturing Noninjectable Products Only",

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for products intended for further manufacturing into noninjectable products. The statement shall follow the proper name in the same size and type of print as the proper name. If the Source Plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, the Source Plasma must be labeled under § 610.40(h)(2)(ii)(E) of this chapter.

(3) The statement “Store at -20°C or colder”: *Provided*, That where plasma is intended for manufacturing into noninjectable products, this statement may be omitted if replaced by a statement of the temperature appropriate for the final product to be prepared from the plasma.

(4) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(5) The donor number or individual bleed number, or both. If plasma is pooled from two or more donors, either all donor numbers, all bleed numbers, or a pool number that is traceable to each individual unit comprising the pool.

(6) The expiration date of the plasma. If plasma intended for manufacturing into noninjectable products is pooled from two or more donors the expiration date is determined from the collection date of the oldest unit in the pool, and the pooling records shall show the collection date for each unit constituting the pool.

(7) A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.

(8) The test for hepatitis B surface antigen used for the results, or the statement “Nonreactive for HB_s Ag by FDA required test”.

(9) When plasma collected from a donor is reactive for the serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphilis.

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(10) Name, address, and license number of the manufacturer.

(11) The statement “Negative by a test for antibody to HIV”, or equivalent statement.

(b) Source Plasma diverted for Source Plasma Salvaged shall be relabeled “Source Plasma Salvaged” as prescribed in § 640.76. Immediately following the proper name of the product, the labeling shall conspicuously state as applicable, “STORAGE TEMPERATURE EXCEEDED -20°C ” or “SHIPPING TEMPERATURE EXCEEDED -5°C ”.

[41 FR 10770, Mar. 12, 1976, as amended at 41 FR 27034, July 1, 1976; 41 FR 35062, Aug. 19, 1976; 47 FR 30969, July 16, 1982; 50 FR 4140, Jan. 29, 1985; 50 FR 35471, Aug. 30, 1985; 53 FR 117, Jan. 5, 1988; 63 FR 16685, Apr. 6, 1998; 66 FR 31165, June 11, 2001]

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacturing of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood and blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or clinical laboratory is qualified to perform the assigned test(s).

(1) The test for hepatitis B surface antigen.

(2) The total plasma or serum protein and the quantitative test for plasma or serum proteins or for immunoglobulins.

(3) The serologic test for syphilis.

(4) A test for antibody to HIV.

(b) Such testing shall not be considered divided manufacturing, which requires two biologics licenses for Source Plasma: *Provided*, That

(1) The results of such tests are maintained by the licensed manufacturer of the Source Plasma whereby such results may be reviewed by a licensed physician as required in § 640.65(b)(2) of

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this chapter and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Center for Biologics Evaluation and Research, Food and Drug Administration.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 55 FR 11013, Mar. 26, 1990; 64 FR 45374, Aug. 19, 1999; 64 FR 56453, Oct. 20, 1999; 66 FR 1837, Jan. 10, 2001]

§ 640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation shall be available to ensure that the shipping temperature requirements of § 600.15 of this title and of § 640.74(b)(2) are being met for Source Plasma intended for manufacture into injectable products.

(2) For each donor, a separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken pursuant to §§ 640.63, 640.65, 640.66, and 640.67, except that negative test results for hepatitis B surface antigen, negative test results for antibody to HIV, and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record: *Provided*, That such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

(4) The certification of the donor's good health as prescribed in § 640.63(b)(3).

(5) If plasma that is reactive to a serologic test for syphilis is issued as prescribed in § 640.65(b)(2)(iv), the distribution records shall indicate by number those units that are reactive.

(b) Each donor record must be directly cross-referenced to the unit(s) of Source Plasma associated with the donor.

(c) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

(d) If a donor has a reaction while on the plasmapheresis premises, or a donor reaction is reported to the center after the donor has left the premises, the donor's record shall contain a full explanation of the reaction, including the measures taken to assist the donor and the outcome of the incident.

[41 FR 10770, Mar. 12, 1976, as amended at 50 FR 4140, Jan. 29, 1985; 53 FR 117, Jan. 5, 1988; 64 FR 45374, Aug. 19, 1999; 67 FR 9587, Mar. 4, 2002]

§ 640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Center for Biologics Evaluation and Research shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

[41 FR 10770, Mar. 12, 1976, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

§ 640.74 Modification of Source Plasma.

(a) Upon approval by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, of a supplement to the biologics license application for Source Plasma, a manufacturer may prepare Source Plasma as a liquid product for a licensed blood derivative manufacturer who has indicated a need for a liquid product.

(b) Source Plasma Liquid shall meet all standards of the frozen Source Plasma except:

(1) Source Plasma Liquid shall be stored in nonleachable containers so that the containers and their components will not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection

against external factors that may cause deterioration or contamination.

(2) Source Plasma Liquid shall be shipped, stored and labeled for storage at a temperature of 10 °C or colder. An exception to the shipping or storage temperature shall be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, based upon his receipt of substantial evidence to support another temperature. Such evidence may be submitted by either the licensed manufacturer of the Source Plasma Liquid or the manufacturer of the final blood derivative product who has requested the Source Plasma Liquid.

(3) The label for the Source Plasma Liquid shall be easily distinguished from that of the frozen product. Color coding shall not be used for this purpose.

(4) The label affixed to each container of Source Plasma Liquid shall contain, in addition to the information required by § 640.70(a) but excluding § 640.70(a)(3), the name of the manufacturer of the final blood derivative product for whom it was prepared.

(5) Source Plasma Liquid shall be inspected immediately prior to issuance. If the color or physical appearance is abnormal, or there is any indication or suspicion of microbial contamination, the unit of Source Plasma Liquid shall not be issued.

[38 FR 32089, Nov. 20, 1973. Redesignated and amended at 41 FR 10770, Mar. 12, 1976; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 59 FR 49351, Sept. 28, 1994; 63 FR 16685, Apr. 6, 1998; 64 FR 56454, Oct. 20, 1999]

§ 640.76 Products stored or shipped at unacceptable temperatures.

(a) *Storage temperature.* (1) Except as provided in paragraph (a)(2) of this section, Source Plasma intended for manufacture into injectable products that is inadvertently exposed (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a storage temperature warmer than –20 °C and colder than +10 °C may be issued only if labeled as “Source Plasma Salvaged.” The label shall be revised before issuance, and appropriate records shall be maintained identifying the units involved, describing

ing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(2) Source Plasma intended for manufacture into injectable products that is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to one episode of storage temperature fluctuation that is warmer than –20 °C and colder than –5 °C for not more than 72 hours is exempt from the labeling requirements of paragraph (a)(1) of this section, provided that the plasma has been and remains frozen solid. Appropriate records shall be maintained identifying the units involved, describing their disposition, explaining fully the conditions that caused the inadvertent temperature exposure, and documenting that the episode of temperature elevation did not exceed 72 hours, that the temperature did not rise to warmer than –5 °C in storage, and that the plasma remained frozen solid throughout the period of elevated temperature. When requested, copies of the records shall be provided to the plasma derivative manufacturer.

(b) *Shipping temperature.* If Source Plasma for manufacture into injectable products is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a shipping temperature warmer than –5 °C and colder than +10 °C, the plasma derivative manufacturer shall label it “Source Plasma Salvaged.” Appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(c) *Relabeling.* If Source Plasma is required to be relabeled as “Source Plasma Salvaged” under paragraph (a)(1) or (b) of this section, the person responsible for the relabeling shall cover the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

[45 FR 80501, Dec. 5, 1980, as amended at 50 FR 4140, Jan. 29, 1985]

Subpart H—Albumin (Human)**§ 640.80 Albumin (Human).**

(a) *Proper name and definition.* The proper name of the product shall be Albumin (Human). The product is defined as a sterile solution of the albumin derived from human plasma.

(b) *Source material.* The source material of Albumin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26286, May 14, 1999]

§ 640.81 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of -5°C or colder. Any other bulk form of the product, exclusive of the sterile bulk solution, to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5°C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5°C or colder.

(e) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated continuously for not less than 10, or more than 11 hours, at an attained temperature of $60\pm 0.5^{\circ}\text{C}$.

(f) *Stabilizer.* Either 0.08 ± 0.016 millimole sodium caprylate, or 0.08 ± 0.016 millimole sodium acetyltryptophanate and 0.08 ± 0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value for the protein concentration of the product as referred to in § 640.84(d).

(g) *Incubation.* All final containers of Albumin (Human) shall be incubated at 20 to 35°C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26286, May 14, 1999; 65 FR 13679, Mar. 14, 2000; 65 FR 52018, Aug. 28, 2000]

§ 640.82 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein concentration.* Final product shall conform to one of the following concentrations: 4.0 ± 0.25 percent; 5.0 ± 0.30 percent; 20.0 ± 1.2 percent; and 25.0 ± 1.5 percent solution of protein.

(b) *Protein composition.* At least 96 percent of the total protein in the final product shall be albumin, as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *pH.* The pH shall be 6.9 ± 0.5 when measured in a solution of the final

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product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Albumin (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27582, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 26286, May 14, 1999]

§ 640.83 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

[42 FR 27582, May 31, 1977]

§ 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter;

(b) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More Than 4 Hours After the Container Has Been Entered.";

(c) The need for additional fluids when 20 percent or 25 percent albumin is administered to a patient with marked dehydration;

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(d) The protein concentration, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

[42 FR 27582, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984; 64 FR 26286, May 14, 1999]

Subpart I—Plasma Protein Fraction (Human)

SOURCE: 42 FR 27583, May 31, 1977, unless otherwise noted.

§ 640.90 Plasma Protein Fraction (Human).

(a) *Proper name and definition.* The proper name of the product shall be Plasma Protein Fraction (Human). The product is defined as a sterile solution of protein composed of albumin and globulin, derived from human plasma.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27583, May 31, 1977, as amended at 64 FR 26286, May 14, 1999]

§ 640.91 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which:

(1) After the heating prescribed in paragraph (e) of this section does not show an increase in the components with electrophoretic mobility similar to that of alpha globulin that amounts to more than 5 percent of the total protein.

(2) Contains less than 5 percent protein with a sedimentation coefficient greater than 7.0 S.

(3) Is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from microorganisms, pyrogens, or other impurities. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of -5°C or colder. Any other bulk form of the product (exclusive of the sterile bulk solution) to be held more than 1 week prior to further processing, shall be stored in clearly identified closed vessels at a temperature of 5°C or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of 5°C or colder.

(e) *Heat treatment.* Heating of the final containers of Plasma Protein Fraction (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of $60\pm 0.5^{\circ}\text{C}$.

(f) *Stabilizer.* Either 0.08 ± 0.016 millimole sodium caprylate, or 0.08 ± 0.016 millimole sodium acetyltryptophanate and 0.08 ± 0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value 5 percent for the protein concentration of the product.

(g) *Incubation.* All final containers of Plasma Protein Fraction (Human) shall be incubated at 20 to 35°C for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, the types of organisms shall be identified as to genus and the material from

such containers shall not be used for further manufacturing.

[42 FR 27583, May 31, 1977, as amended at 64 FR 26286, May 14, 1999]

§ 640.92 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein concentration.* The final product shall be a 5.0 ± 0.30 percent solution of protein.

(b) *Protein composition.* The total protein in the final product shall consist of at least 83 percent albumin, and no more than 17 percent globulins. No more than 1 percent of the total protein shall be gamma globulin. The protein composition shall be determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *pH.* The pH shall be 7.0 ± 0.3 when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium concentration.* The sodium concentration of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Potassium concentration.* The potassium concentration of the final product shall not exceed 2 milliequivalents per liter.

(f) *Heat stability.* A final container sample of Plasma Protein Fraction (Human) shall remain unchanged, as determined by visual inspection, after heating at 57°C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27583, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 64 FR 26286, May 14, 1999; 65 FR 13679, Mar. 14, 2000]

§ 640.93 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of

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the final product prescribed in § 610.53 of this chapter.

§ 640.94 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma, and the sodium concentration in terms of a value or a range in milliequivalents per liter.

(b) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More than 4 Hours After the Container Has Been Entered."

[42 FR 27583, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984; 64 FR 26286, May 14, 1999]

Subpart J—Immune Globulin (Human)

§ 640.100 Immune Globulin (Human).

(a) *Proper name and definition.* The proper name of this product shall be Immune Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human plasma.

(b) *Source material.* The source material of Immune Globulin (Human) shall be plasma recovered from Whole Blood prepared as prescribed in §§ 640.1 through 640.5, or Source Plasma prepared as prescribed in §§ 640.60 through 640.76.

(c) *Additives in source material.* The source material shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 64 FR 26287, May 14, 1999]

§ 640.101 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12x75

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mm. stoppered glass tube at 57 °C for 4 hours.

(b) *pH.* The pH of final container material shall be 6.8 ±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 640.104(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this subchapter, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

[38 FR 32089, Nov. 20, 1973; 48 FR 13026, Mar. 29, 1983, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 51 FR 15611, Apr. 25, 1986; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

§ 640.102 Manufacture of Immune Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of –10 °C or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0 °C or lower.

(d) *Determination of the lot.* Each lot of Immune Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45 °C, and after sterilization the product shall not be exposed to temperatures above 32 °C for more than 72 hours.

[38 FR 32089, Nov. 20, 1973, as amended at 50 FR 4140, Jan. 29, 1985; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999; 65 FR 13679, Mar. 14, 2000; 65 FR 52018, Aug. 28, 2000]

§ 640.103 The final product.

(a) *Final solution.* The final product shall be a 16.5 ±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 96 percent of the total protein shall be immunoglobulin G (IgG), as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

[38 FR 32089, Nov. 20, 1973, as amended at 64 FR 26287, May 14, 1999]

§ 640.104 Potency.

(a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a temperature above 5 °C the antibody level tests shall be performed after such storage with a sample of the stored material.

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will

advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(3) A poliomyelitis Type 1, Type 2, or Type 3 neutralizing antibody level that, when compared with that of a reference material designated by the Center for Biologics Evaluation and Research, Food and Drug Administration, as indicated in paragraph (c) of this section, demonstrates adequate potency. The Director, CBER, shall notify manufacturers when a new reference material will be used and will advise manufacturers of an appropriate antibody level taking into account a comparison of the new reference material to the previous reference material.

(c) *Reference materials.* The following reference materials shall be obtained from the Center for Biologics Evaluation and Research:

(1) Reference Immune Globulin for correlation of measles antibody titers.

(2) Reference Immune Globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

[38 FR 32089, Nov. 20, 1973, as amended at 39 FR 9661, Mar. 13, 1974; 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 63 FR 16685, Apr. 6, 1998; 64 FR 26287, May 14, 1999]

Subpart K [Reserved]

Subpart L—Alternative Procedures

§ 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with § 601.12 of this chapter. However, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

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(b) FDA will publish a list of approved alternative procedures and exceptions periodically in the FEDERAL REGISTER.

[55 FR 10423, Mar. 21, 1990, as amended at 62 FR 39903, July 24, 1997]

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

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660.55 Labeling.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372; 42 U.S.C. 216, 262, 263, 263a, 264.

CROSS REFERENCES: For U.S. Customs Service regulations relating to viruses, serums, and toxins, see 19 CFR 12.21–12.23. For U.S. Postal Service regulations relating to the admissibility to the United States mails see parts 124 and 125 of the Domestic Mail Manual, that is incorporated by reference in 39 CFR part 111.

Subpart A—Antibody to Hepatitis B Surface Antigen

§ 660.1 Antibody to Hepatitis B Surface Antigen.

(a) *Proper name and definition.* The proper name of this product shall be Antibody to Hepatitis B Surface Antigen. The product is defined as a preparation of serum containing antibody to hepatitis B surface antigen.

(b) *Source.* The source of this product shall be plasma or blood, obtained aseptically from animals immunized with hepatitis B surface antigen, which have met the applicable requirements of § 600.11 of this chapter, or from human donor whose blood is positive for hepatitis B surface antigen.

[40 FR 29711, July 15, 1975]

§ 660.2 General requirements.

(a) *Processing.* The processing method shall be one that has been shown to consistently yield a specific and potent final product free of properties which would adversely affect the test results when the product is tested by the methods recommended by the manufacturer in the package enclosure.

(b) *Ancillary reagents and materials.* All ancillary reagents and materials supplied in the package with the product shall meet generally accepted standards of purity and quality and shall be effectively segregated and otherwise manufactured in a manner (such as heating at 60 °C. for 10 hours) that will reduce the risk of contaminating the product and other biological products. Ancillary reagents and materials accompanying the product which are used in the performance of the test as described by the manufacturer's recommended test procedures shall have been shown not to adversely affect the